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EXAMINER	
BRISTOL, LYNN ANNE	
ART UNIT	PAPER NUMBER
1643	

SHORTENED STATUTORY PERIOD OF RESPONSE	NOTIFICATION DATE	DELIVERY MODE
3 MONTHS	02/22/2007	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Notice of this Office communication was sent electronically on the above-indicated "Notification Date" and has a shortened statutory period for reply of 3 MONTHS from 02/22/2007.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/511,273	KOSMATOPOULOS ET AL.	
	Examiner	Art Unit	
	Lynn Bristol	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *16 December 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-29* is/are pending in the application.

4a) Of the above claim(s) *6 and 10-29* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5 and 7-9* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☒ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/21/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-29 are all the pending claims for this application.

2. Claims 1-13 have been amended and new claims 14-29 added by amendment in the Response of 12/16/06.

The amendment of Claims 6-9 to recite proper claim dependency is acknowledged. The amendment of Claims 7-9 to recite a composition comprising multiple peptides or chimeric polypeptides finds support in the specification at [0036-0038], however, the amendment of Claim 8 to recite that the composition comprises both a peptide and a polynucleotide encoding the peptide raises an issue of new matter discussed infra.

Claims 10-13 have been restated as method claims to bring the claims into compliance under 35 U.S.C. 101. Applicants allege on p. 7 of the Response that new Claims 14-29 "are supported by original Claims 7-13". The Examiner submits that new claims 14 and 16-29 are supported by the cancelled subject matter of Claims 7-13, but that new Claim 15 raises an issue of new matter as the same reason for Claim 8 supra.

All of the claims have been entered.

Election/Restrictions

3. Applicant's election with traverse of Group I (Claims 1-5 and 7-9) in the reply filed on 12/16/06 is acknowledged. The traversal set forth on p. 8, ¶2-4 of the Reply is three-fold:

a) first at ¶2, Applicants allege "there is no disclosure nor suggestion in the cited prior art to combine their technical features in the manner of the present invention and therefore the statement of lack of unity made by the Office based on obviousness is not properly supported."

This is not found persuasive because Applicant has not provided any technical or legal arguments why the lack of unity restriction is improper over the cited references. Further and as discussed infra, the Examiner has identified additional prior art reference(s) teaching and/or suggesting the special technical feature of the invention.

b) second at ¶3, Applicants traversal is on the on ground that because the IPEA found there to be a unity of invention amongst the claims, the Examiner is obliged to apply the same standard under PCT Article 27(1).

This is not found persuasive because 37 CFR 1.499 (MPEP 1893.03(d)) provides that an examiner **may** require the restriction of claims for a national stage application that lacks unity of invention under §1.1475.

c) third at ¶3, Applicants allege "that the Office has not shown that a burden exists in searching the entire application."

The Examiner submits that pursuant to PCT 13.1, the criteria for unity of invention is the demonstration of a single general inventive concept relating to one invention only or to a group of inventions. Thus the Examiner is under no obligation to establish a search burden for claims or inventions in a 371 national stage application, where as in the present case, the Examiner has established that the single inventive concept or "special technical feature" is not a contribution over the prior art.

For all of the foregoing reasons, the restriction is maintained and made final.

4. Claims 6 and 10-29 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected inventions, there being no allowable generic or linking claim. Applicant timely traversed the restriction requirement in the reply filed on 12/16/06.

5. Claims 1-5 and 7-9 are all the pending claims under examination of the merits.

Information Disclosure Statement

6. The U.S. patent and non-patent literature references cited in the IDS of 10/21/04 have been considered and entered.

Oath/Declaration

7. The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because:

Non-initialed and/or non-dated alterations have been made to the oath or declaration. See 37 CFR 1.52(c).

Specification

8. The Abstract of Disclosure is objected for the following reasons:

Applicant is reminded of the proper language and format for an abstract of the disclosure.

The abstract should be in narrative form and generally limited to a single paragraph on a separate sheet within the range of 50 to 150 words. It is important that the abstract not exceed 150 words in length since the space provided for the abstract on the computer tape used by the printer is limited. The form and legal phraseology often used in patent claims, such as "means" and "said," should be avoided. The abstract should describe the disclosure sufficiently to assist readers in deciding whether there is a need for consulting the full patent text for details.

9. The disclosure is objected to because of the following informalities:

a) The application is objected to because of alterations on p. 1 which have not been initialed and/or dated as is required by 37 CFR 1.52(c).

b) The disclosure is objected to because it contains embedded hyperlinks and/or other form of browser-executable code. See p. 4, lines 16-17 and 19. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

c) The following guidelines illustrate the preferred layout for the specification of a utility application. These guidelines are suggested for the applicant's use.

Arrangement of the Specification

As provided in 37 CFR 1.77(b), the specification of a utility application should include the following sections in order. Each of the lettered items should appear in upper case, without underlining or bold type, as a section heading. If no text follows the section heading, the phrase "Not Applicable" should follow the section heading:

(a) TITLE OF THE INVENTION.
(b) CROSS-REFERENCE TO RELATED APPLICATIONS.
(c) STATEMENT REGARDING FEDERALLY SPONSORED RESEARCH OR DEVELOPMENT.
(d) THE NAMES OF THE PARTIES TO A JOINT RESEARCH AGREEMENT.
(e) INCORPORATION-BY-REFERENCE OF MATERIAL SUBMITTED ON A COMPACT DISC.
(f) BACKGROUND OF THE INVENTION.
(1) Field of the Invention.

(2) Description of Related Art including information disclosed under 37 CFR 1.97 and 1.98.
(g) BRIEF SUMMARY OF THE INVENTION.
(h) BRIEF DESCRIPTION OF THE SEVERAL VIEWS OF THE DRAWING(S).
(i) DETAILED DESCRIPTION OF THE INVENTION.

Notably, Applicants have not provided a Brief Description of the Drawings (Figures 1-6) anywhere in the originally filed specification. See MPEP § 608.01(f). A reference to and brief description of the drawing(s) as set forth in 37 CFR 1.74 is required.

Additionally, because Figure 1 is polypeptide sequence and the sequence identifier is not provided with the original figure, pursuant to 37 CFR 1.821(c), a sequence identifier must be appear for any amino acid sequences of four or more residues or nucleotide sequences of 10 or more nucleotides. Thus Applicants are required to identify the sequence by SEQ ID NO in the amended specification or to file a revised drawing sheet for Figure 1 identifying where any corrections have been made.

Appropriate correction is required.

Claim Objections

10. Claim 9 is objected to because of the following informalities: the phrase "selected from a group" contains a typographical error and should recite "selected from the group". Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

11. Claims 1-5 and 7-9 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a) Claims 1-5 and 7-9 are indefinite for the recitation "EphA2" because it is not clear what molecule of the infinite molecules is being claimed. Amending Claims 1 and 3 to recite "Eck tyrosine kinase receptor" would obviate the rejection.

b) Claims 1-5 and 7-9 recite the limitation "the EphA2 antigen" in Claims 1 and 3. There is insufficient antecedent basis for this limitation in either of the independent claims.

c) Claims 1-5 and 7-9 are indefinite for the recitation "the EphA2 antigen" because in Claims 1, 3, 4 and 9 it is not clear what the EphA2 antigen is or whether the intended scope is for the EphA2 protein. The specification describes the peptides being derived from the EphA2 protein. The specification does not define the entire EphA2 molecule as being antigenic, but one of skill in the art would understand from the disclosure that the EphA2 protein contains antigenic regions from which the peptides are derived.

d) Claims 4 and 5 recite the limitation "said peptide". There is insufficient antecedent basis for this limitation in the claims because in depending from Claim 3, it is unclear whether "said peptide" refers to the immunogenic peptide or the peptide fragment used to produce the immunogenic peptide.

e) Claims 3 and 4 are indefinite because it is not clear if the starting peptide or the peptide from which the "immunogenic peptide" is derived is non-immunogenic, and that substituting amino acid(s) for the starting peptide is what confers both 1) immunogenicity and 2) increased MHC I allelic affinity.

f) The term "increases " in claim 3 is a relative term which renders the claim indefinite. The term "increases" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. Does an increase in affinity reflect a change in the relative affinity (RA) or the rate of dissociation (DC50), which reflects the stability of the peptide(s), for the MHC I allele, etc.?

g) Claims 8 and 9 are indefinite for the phrase "comprising at least one selected from" because it is not clear what is being selected. Do Applicants mean one or more of the same or another peptide(s) is being further selected for the composition?

h) Claim 9 is indefinite for lack of clarity in describing the structural properties of the chimeric polypeptide, because it is not clear what "a copy" of a peptide is referring to. The specification simply defines a chimeric polypeptide as "comprising one or more copies of an immunogenic peptide" [0038].

i) Claims 8 and 9 are indefinite for the phrases "other immunogenic peptides" and "another immunogenic peptide", respectively, because it is not clear if the other peptide should be derived from the EphA2 protein or from an unrelated antigenic protein, and if the latter case, then what other immunogenic peptides are contemplated?

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Written Description

12. Claims 8 and 9 are rejected under 35 U.S.C. 112, first paragraph for reciting new matter.

Claim 8 is drawn to a composition comprising at least one immunogenic peptide constituting a T epitope presented by MHC I, and consisting of a fragment of 8 to 11 consecutive amino acids of the EphA2 antigen (hereinafter referred to an the "EphA2 peptide") and a multiepitope composition comprising a peptide from the Markush group for other immunogenic peptides and polynucleotides encoding the other immunogenic peptides. Claim 9 is drawn a composition comprising at least one immunogenic EphA2 peptide and a chimeric polypeptide comprising a peptide from the Marksuh group for a copy of the immunogenic EphA2 peptide and a copy of another immunogenic peptide.

The specification does not provide literal support for the claimed compositions and thus the claims are drawn to new matter.

The specification discloses the following distinct compositions:

- compositions comprising at least one immunogenic peptide in accordance with the invention (p. 7, lines 5-6);
- compositions comprising a nucleic acid molecule encoding the inventive peptide (p. 7, lines 6-7);

- multiepitope compositions comprising one or more other immunogenic epitope(s). These other epitopes may be derived from EphA2 or from one or more other antigens (p. 7, lines 10-12);
- compositions comprising at least one chimeric polypeptide comprising one or more copies of an immunogenic peptide in accordance with the invention and one or more copies of at least one other immunogenic epitope (p. 7, lines 21-26);
- compositions comprising nucleic acid molecules encoding chimeric polypeptide in accordance with the invention (p. 7, line 32).

The specification does not support compositions comprising both the EphA2 immunogenic peptide and a nucleic acid or polynucleotide encoding other immunogenic peptides in the same composition (Claim 8). The specification does not support nucleic acids encoding "other immunogenic peptides" (Claim 8). The specification does not support compositions comprising both the EphA2 immunogenic peptide and a chimeric polypeptide (Claim 9).

Enablement

13. Claim 1-5 and 7-9 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the HLA-restricted, EphA2-derived CTL-specific immunogenic peptides p58: IMNDMPIYM (SEQ ID NO: 4); p546: VLLLVLAGV (SEQ ID NO: 6); p550: VLAGVGFFI (SEQ ID NO: 7); p883: TLADFDPRV (SEQ ID NO: 8) and p61Y: YMPIYMYSV (SEQ ID NO: 9), and the p58 and and p550 peptides triggering CTL

in vivo in HLA-A 0201 transgenic HHD mice and in vitro in healthy humans, and an in vivo amplification of p58-sepcific CD8+ T cells in prostate cancer patients (and in vitro restimulation of PBMCs with the peptide), although melanoma, prostate, and lung cancer patients presented frequencies of CD8+ T cells specific for p58 and p550 comparable to healthy donors, does not reasonably provide enablement for the peptides producing an immunogenic response in just any cancer patient because tolerance to normally expressed EphA2 must be overcome, or for multiepitope compositions comprising different immunogenic EphA2 peptides combined with immunogenic peptides from other tumor antigens, or polyepitopic constructs such as chimeric polypeptides comprising the EphA2 peptides in combination with other tumor peptides, or nucleotides encoding any one EphA2 peptide or in combination with other tumor antigen peptides. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in In re Wands, 8 USPQ2d 1400 (Fed. Cir. 1988). They include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability of the art, the breadth of the claims, the quantity of experimentation which would be required in order to practice the invention as claimed.

A) Disclosure of the specification and prior art is not enabling for inducing MHC Class I-restricted (HLA), peptide-specific T cells with any EphA2-based peptide alone or in combination with other immunogenic peptides or nucleic acids encoding the same

Nature of the invention

Claims 1-5 and 7-9 are drawn to an MHC Class I (HLA) restricted, T cell-specific peptides from the EphA2 protein being from 8-11 consecutive amino acids in length, where the peptide is p58: IMNDMPIYM (SEQ ID NO: 4); p546: VLLLVLAGV (SEQ ID NO: 6); p550: VLAGVGFFI (SEQ ID NO: 7); or p883: TLADFDPRV (SEQ ID NO: 8), where the peptide is derived from a fragment of from 8-11 consecutive amino acids of the EphA2 protein and comprising amino acid substitutions that increase the affinity of the peptide for the MHC I allele, where the substituted peptide is N-terminal substituted with a tyrosine residue, where the N-terminal substituted peptide is p61Y of SEQ ID NO:9, and compositions comprising at least of the immunogenic peptides, further comprising a mutliepitope composition comprising other immunogenic peptides or polynucleotides encoding the other immunogenic peptides, or compositions further comprising a chimeric polypeptide comprising a copy of an EphA2 peptide or a copy of another immunogenic peptide.

Disclosure of the specification

The specification teaches identifying and making MHC Class I (HLA) restricted, CTL-specific peptides for EphA2 protein based on selecting the peptides which have all or part of the primary anchor motif corresponding to an MHC allele using databases

listing known anchor motifs (p. 4, lines 9-20). The disclosed peptides are p58: IMNDMPIYM (SEQ ID NO: 4); p546: VLLLVLAGV (SEQ ID NO: 6); p550: VLAGVGFFI (SEQ ID NO: 7); p883: TLADFDPRV (SEQ ID NO: 8) and p61Y: YMPIYMYSV (SEQ ID NO: 9). The specification teaches that all the peptides had a high affinity for HLA (Table 1). The specification teaches that p58 and p550 are immunogenic in transgenic HHD mice, that peptide-specific murine CTL cell lines responded to COS-7 cells coexpressing HLA-A 0201 and EphA2 and to EphA2-positive human tumor cells of various origin (renal cell, lung, and colon carcinoma and sarcoma). The p58 and p550 peptides stimulated CD8+ T cells from healthy normal donor PBMCs and the T cells recognized EphA2-positive human tumor cells (CACO-2 (colon cancer) and 1355 (lung cancer)) in an HLA-restricted manner. Finally, EphA2-specific CD8+ T cells were detected in the PBMC from a prostate cancer patient.

Applicants have not provided any evidence showing EphA2 peptidogenic-specific CTL induction in any animal tumor model. In the absence of working examples, one skilled in the art could not even predict and extrapolate that any EphA2-derived peptide or a composition comprising at least one peptide, could reproducibly induce a specific T cell response in any healthy animal or patient much less an animal or patient having an EphA2-expressing tumor. Further Applicants have not shown that inclusion of widely differing epitopes from tumor antigens in a composition comprising a multiepitope composition comprising another immunogenic peptide, or a composition comprising a multiepitope composition comprising a nucleic acid encoding another immunogenic peptide, or a composition comprising a chimeric polypeptide, could reproducibly trigger

polyspecific CTL responses against a large number of tumors in a tumor immunotherapy strategy as broadly encompassed by the claims.

Applicants are invited to supplement the record with evidence showing a correlative effect for any EphA2-derived peptide vaccine or any composition comprising a multiepitope polypeptide or a chimeric polypeptide in producing MHC I-restricted, EphA2 epitope-specific CTL induction as broadly encompassed by the claims.

ii) Disclosure in the prior art.

In general, the art of synthesizing functional equivalents of naturally occurring proteins is very unpredictable in nature. Although Schirle et al. (J. Immunol. Methods. 2001; 257: 1-16), for example, teaches that several computer algorithms are now available for use in predicting the structures of synthetic peptides that bind MHC molecules, Schirle et al. teaches, "the identified epitopes still have to pass the ultimate test: they have to prove to be useful in the in vivo situation" (page 11, paragraph bridging columns 1 and 2).

Moreover Anderson et al. (Tissue Antigens. 2000 Jun; 55 (6): 519-531) teaches there is poor correspondence between predicted and experimental binding of peptides to class I MHC molecules; see entire document (e.g., the abstract). Andersen et al. teaches, while knowledge of the peptide binding motifs of individual class I MHC molecules permits the selection of potential peptide antigens, there is no strong correlation between actual and predicted binding when using predictive computer algorithms, and therefore the peptide binding assay remains an important step in the

identification of cytotoxic T lymphocyte (CTL) epitopes, which cannot be substituted by predictive algorithms (abstract).

Furthermore, Feltkamp et al. (Mol. Immunol. 1994 Dec; 31 (18): 1391-1401) teaches, while efficient binding of peptide epitopes to MHC class I molecules is required to elicit an immune response against the peptide epitope or the intact antigen, an increased binding affinity does not consistently and reproducibly relate to a peptide epitope's immunogenicity, i.e., its ability to elicit a peptide- and antigen-specific immune response; see entire document (e.g., the abstract). Feltkamp et al. teaches that other factors, in addition to its binding affinity for an MHC molecule, determine whether a peptide epitope, or analogue thereof, will be able to stimulate an effective immune response; see, e.g., the abstract.

With respect to the general state of the art for peptide vaccine induction of CTLs, Beier et al. (USPN 2004/0037840; published 2/26/2004; filed 10/26/2001) discloses:

> "It has been clearly demonstrated by several groups that tumour specific cytotoxic T cells (CTL's) are present in many tumours. These CTL's are termed tumour infiltrating lymphocytes (TIL's). However, these cells are somehow rendered non-responsive or anergic by several different possible mechanisms including secretion of immunosuppressive cytokines by the tumour cells, lack of co-stimulatory signals, down regulation of MHC class I molecules etc. There has been many attempts to isolate the tumour specific HLA class I bound peptides recognised by TILs, and in some cases it has also been successful (e.g. peptides from the melanoma associated antigens). Such peptides have been used to induce a tumour specific immune response in the host, but the practical use of tumour specific peptides in vaccines is restricted to a limited segment of the population due to the narrow HLA class I binding specificity of the peptides. Furthermore, it is usually relatively difficult to evoke a CTL response in vivo using synthetic peptides due to the low biological half-life of these substances as well as the difficulties with exogenous priming of MHC class I molecules." [0023-0024]

Finally, Applicants teach in their own publication (Can. Res. 63:8476-8480 (2003)) that because EphA2 is expressed at low levels by normal tissues such as lung, kidney, skin, ovaries, and even thymus, two questions are raised that are common for all of the ubiquitously expressed antigens:

> "a) is there tolerance to EphA2, and if there is, how can we recruit in vivo anti-EphA2 CTL with high avidity; and b) what is the risk of autoimmunity after vaccination with EphA2 CTL epitopes?" (p. 8480, Col. 1, ¶3).

Applicants have not answered these questions in the specification or extended our understanding of the status of the art for the inventive peptides with respect to these inherent risks associated with peptide vaccines.

2) Undue experimentation is required to demonstrate a CTL response to just any EphA2 peptides under in vitro much less in vivo conditions.

One cannot extrapolate the teaching of the specification to the claimed invention because the specification provides no exemplification of or guidance on how to use the claimed peptide(s) for active immunotherapy in vivo. The goal of tumor vaccination is the induction of tumor immunity to prevent tumor recurrence and to eliminate residual disease. However, Ezzell (J. NIH Res, 1995, 7:46-49) reviews the current thinking in cancer vaccines and states that tumor immunologists are reluctant to place bets on which cancer vaccine approach will prove effective in the long run (see the entire document, particularly last paragraph) and further states that no one is very optimistic that a single peptide will trigger an immune response strong enough to eradicate tumors

or even to prevent the later growth of micrometastases among patients whose tumors have been surgically removed or killed by radiation or chemotherapy (p 48, ¶6).

The Examiner appreciates that "some experimentation does not necessarily equate to undue experimentation", but to advance the in vitro experiments disclosed in the specification into preclinical animal testing for entry into phase one clinical trials in human patients would not involve routine experimentation (MPEP 2164.06, "The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." (In re Wands, 858 F.2d 731, 737, 8 USQP2d 1400, 1404 (Fed. Cir. 1988) (citing In re Angstadt, 537 F.2d 489, 502-04, 190 USPQ 214, 217-19 (CCPA 1976)).

Neither the specification nor prior art are enabling for just any peptide as broadly encompassed by the claims at inducing an MHC Class I-restricted, EphA2 epitope-specific T cell.

B) Any EphA2 peptide having any amino acid substitution or any EphA2 peptide being N-terminally substituted with a tyrosine residue is not enabled for inducing an CTL response either in vitro or in vivo.

Claims 3 and 4 are broadly drawn to the peptide having any amino acid substitution or combination of amino acid substitutions occurring within a fragment of 8-11 consecutive amino acids from the EphA2 protein, and where the peptide retains the properties of being MHC-restricted, CTL-epitope specific, has increased affinity for an MHC I allele and where the N-terminal amino acid residue is tyrosylated. As discussed

supra, the only disclosure in the specification for a peptide meeting all of the limitations of claims 3 and 4 is the peptide of SEQ ID NO:9. Thus, the specification does not enable just any peptides that are modified in amino acid sequences compared to the parent peptide sequence or replacing just any N-terminal residue of any peptide with a tyrosine in order to accomplish the endpoint of the peptide being immunogenic for CTLs.

The claims are not commensurate in scope with the enablement provided in the specification. The specification does not support the broad scope of the claims which encompass all modifications to the peptide sequence because the specification does not disclose the following:

The general tolerance to modification and extent of such tolerance;

The specific positions and regions of the sequence(s) which can be predictably modified and which regions are critical; and

The specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed protein in manner reasonably correlated with the scope of the claims broadly including any number of additions, deletions, or substitutions. The scope of the claims must bear a reasonable correlation with the scope of enablement. See In re Fisher, 166 USPQ 19 24 (CCPA 1970).

Without such guidance, the changes which can be made in the protein's structure and still maintain biological activity is unpredictable and the experimentation left to those

skilled in the art is unnecessarily and improperly extensive and undue. See Amgen, Inc. v. Chugai Pharmaceutical Co. Ltd., 927 F,2d 1200, 18 USPQ 1016 (Fed. Cir. 1991) at 18 USPQ 1026 1027 and Ex parte Forman, 230 USPQ 546 (BPAI 1986).f

Further protein chemistry is probably one of the most unpredictable areas of biotechnology. For example, the replacement of a single lysine at position 118 of the acidic fibroblast growth factor by a glutamic acid led to a substantial loss of heparin binding, receptor binding, and biological activity of the protein (see Burgess et al, Journal of Cell Biology Vol 111 November 1990 2129-2138). In transforming growth factor alpha, replacement of aspartic acid at position 47 with asparagine, did not affect biological activity while the replacement with serine or glutamic acid sharply reduced the biological activity of the mitogen (see Lazar et al Molecular and Cellular Biology Mar 1988 Vol 8 No 3 1247-1252).

Replacement of the histidine at position 10 of the B-chain of human insulin with aspartic acid converts the molecule into a superagonist with 5 times the activity of nature human insulin. Schwartz et al, Proc Natl Acad Sci USA Vol 84:6408-6411 (1987). Removal of the amino terminal histidine of glucagon substantially decreases the ability of the molecule to bind to its receptor and activate adenylate cyclase. Lin et al Biochemistry USA Vol 14:1559-1563 (1975).

These references demonstrate that even a single amino acid substitution or what appears to be an inconsequential chemical modification, will often dramatically affect the biological activity of the protein.

Therefore, in view of the lack of guidance, lack of examples for peptides having any amino acid substitution or an N-terminal substitution with a tyrosine residue confering increased affinity for an MHC allele, and lack of predictability associated with regard to producing and using the myriad peptides encompassed in the scope of the claims, one skilled in the art would be forced into undue experimentation in order to practice the broadly claimed invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

14. Claims 1, 2 and 7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Powell et al. (USPN 20070031882; with priority filing date 2/15/2002) in view Parker et al. (J. of Immunol. 152:163, 1994; cited in the 892 form of 10/13/06).

The interpretation of Claims 1, 2 and 7 is discussed supra.

It would have been prima facie obvious to have produced the immunogenic MHC I-restricted, T-epitope peptides from the EphA2 protein over Powell in view of Parker. Applicants are reminded that because the claims are not restricted to a disease or disorder in which the immunogenic peptide should be applied, that peptides of Powell that are directed to treating HIV/AIDS would read on the instant claims.

Powell discloses the ephrin kinase or EphA2 protein [0012, SEQ ID NO:2], and using immunogenic peptides to produce antibodies for treating HIV/AIDs [0009- 0010; 0183-0185; 0274]. Powell teaches methods for treating subjects with B- epitope peptides from the EphrinA2 protein [0210]. Powell teaches the EphrinA2 protein corresponding to SEQ ID NOS: 4, 6, 7 and 8. Powell does not disclose identifying or using T epitope peptides derived from the EphA2 protein, but Parker rectifies these deficiencies.

Parker teaches methods (BIMAS program) to identify peptides potentially capable of binding to HLA-A*0201 and selecting those with CTL-inducing properties.

One skilled in the art at the time the invention was made would have been motivated to have produced the instant claimed peptide and been assured of reasonable success in doing so based on the combined discloses of Powell and Parker because Powell discloses using immunogenic Epha2 derived peptides to produce antibodies in treating HIV/AIDs and where Powell was in possession of the entire ephrin A2 protein and T-epitopes were inherent to the EphA2 protein, Parker discloses dominant anchor residues important in the HLA molecule for selecting T-cell peptide epitopes using the BIMAS program, and Parker discloses examples of epitopes ranging

from antigenic proteins from viruses such as HTLV and HIV and endogenous peptides (Table VII) selected for HLA restriction and CTL-inducing properties for immunotherapy. One skilled in the art would have been reasonably assured of success in producing the T-epitopes from the EphA2 proteins because the protein sequence and peptide epitopes for the EphA2 protein were already disclosed by Powell and because Parker provides further support for identifying T-epitopes with the properties of being HLA-restricted and immunogenic for T cells in treating HIV infections.

For all of the foregoing reasons, the claims were prima facie obvious at the time the invention was made over Powell and Parker.

15. Claims 1, 2 and 7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lindberg et al (Mol. Cell Biol. 10(12):6316-6324 (1990); cited in the IDS of 10/21/2004) in view Parker et al. (J. of Immunol. 152:163, 1994; cited in the 892 form of 10/13/06) and Renkvist et al. (Cancer Immunol. Immunother. 50:3-15 (2001); cited in the 892 form of 10/13/06).

The interpretation of Claims 1, 2 and 7 is discussed supra.

It would have been prima facie obvious to have produced the immunogenic MHC I-restricted, T-epitope peptides from the EphA2 protein over Lindberg in view of Parker and Renkvist.

Lindberg teaches the cloning and amino acid sequence of EphA2, expression of the protein on epithelial cells and the overexpression of the protein associated in tumorigenesis. Lindberg teaches the EphrinA2 protein corresponding to SEQ ID NOS:

4, 6, 7 and 8. Lindberg teaches that NIH-3T3 cells overexpressing the eph gene acquire tumorigenic ability in nude mice suggesting the role of the molecule in oncogenesis (p. 6323, Col. 2). Lindberg does not disclose identifying or using T epitope peptides derived from the EphA2 protein, but Parker and Renkvist rectify these deficiencies.

The interpretation of Parker is discussed supra.

Renkvist teaches numerous tumor-associated antigens that are recognized by T cells and the HLA-restricted T-cell epitopes (peptides) associated with the antigens.

One skilled in the art would have been motivated and been assured of reasonable success in having produced the T-epitope peptides from EphA2 at the time the invention was made based on the combined disclosures of Lindberg, Parker and Renkvist. The motivation to obtain T-epitope peptides would have been based on the oncogenicity of the eph gene according to Lindberg and the success in producing T-epitope peptides for specific CTL-induction based on the combined disclosures of Parker and Renkvist. Further one skilled in the art would have been reasonable assured of success in generating the peptides because of the available technology and the large number of T-eptitopes that had been identified through art-recognized processes as taught by Parker and Renkvist which had been raised against endogenous proteins and tumor antigens for immunotherapeutic use.

For all of the foregoing reasons, the instant claimed immunogenic peptide was prima facie obvious at the time the invention was made in view of Lindberg, Parker and Renkvist.

Conclusion

16. No claims are allowed.

17. Sequence search of commercial protein sequence databases for the peptide of SEQ ID NO: 9 (p61y) did not identify any sequences having 100% identity with the peptide. The closest prior art reads on the parent peptide having the unsubstituted N-terminal amino acid residue corresponding to p61 of SEQ ID NO:5.

18. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lynn Bristol whose telephone number is 571-272-6883. The examiner can normally be reached on 8:00-4:00, Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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